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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,470	01/07/2005	Thomas Tuschl	2923-673	5503

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EXAMINER

SHIN, DANA H

ART UNIT	PAPER NUMBER
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1635

NOTIFICATION DATE	DELIVERY MODE
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06/27/2007

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/520,470	TUSCHL ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 22-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 and 32-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 January 2005 and 03 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1-7-2005</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Election/Restrictions

Applicant's election of claims 1-21 in the reply filed on June 4, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of Claims

Claims 1-38 are pending. Claims 22-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant has added new claims, claims 32-38, which read on the elected invention. Accordingly, claims 1-21 and 32-38 are currently under examination on the merits.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in the European Patent Office on July 10, 2002 and August 23, 2002. It is noted, however, that applicant has not filed certified copies of the EPO 02015532.1 and EPO 02018906.4 applications as required by 35 U.S.C. 119(b).

Since it cannot be determined whether the disclosure of the prior-filed above foreign applications provide adequate support or enablement in the manner provided by the first

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paragraph of 35 U.S.C. 112 for one or more claims of this application, the benefit of an earlier filing date is granted only insofar as the filing date of PCT/EP03/07516, that is, July 10, 2003.

Applicant is strongly encouraged to submit certified copies of the foreign priority applications to overcome any prior art rejections applied herein.

Claim Objections

Claim 1 is objected to because of the following informalities: It appears that "contacting a target transcript" recited in line 2 should be "contacting the target transcript" or "contacting said target transcript". Appropriate correction is required.

Claim 38 is objected to for missing a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 14, 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 20-21 recite "wherein at least the 14-20 5' most nucleotides are substantially complementary to said target transcript". The term "substantially" is not defined either in the specification or in the claims, and therefore, one of ordinary skill in the art cannot

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ascertain the degree of sequence complementarity claimed in the instant case because the term "substantially" is a relative term.

Claim 14 recites the limitation "said association" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, because the word "association" is not recited in claim 13.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-21, and 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the expression of a target transcript with a single-stranded RNA molecule *in vitro*, does not reasonably provide enablement for a method for inhibiting the target transcript expression *in vivo* therapeutic applications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not

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be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the instant case, claims 10, 17-21, and 37 read strictly on *in vivo* methods and a composition for *in vivo* purpose, while claims 1-8, 11-16, and 32-38 embrace both *in vitro* methods and *in vivo* therapeutic methods.

With regard to the claimed methods, the specification provides *in vitro* examples wherein a single-stranded RNA inhibits target transcript expression in human HeLa cell extracts; however, it is silent about *in vivo* working examples. The lack of *in vivo* examples in the instant case prompts the question whether the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art would have necessitated undue experimentation to practice the entire scope of the claimed invention at the time the invention was made.

As of the earliest filing date sought in the instant application, therapeutic use of nucleic acid molecules was considered highly unpredictable. See Opalinska et al. (*Nature Reviews*, 2002, 1:503-514).

On page 511, Opalinska et al. teach the unpredictability of nucleic acid molecules to modulate the expression of their intended targets *in vivo* as following:

“Nucleic-acid-mediated gene silencing has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA....Accordingly, mRNA targeting is largely a random process, which accounts for the many experiments in which the addition of an antisense nucleic acid yields no effect on expression.”

As evidenced by the post-dated reference by Schmidt (*Nature Biotechnology*, March 2007, 25:273-275), delivering siRNAs or oligonucleotides into the appropriate target cell or tissue still remains problematic in the art, and therefore the unpredictability of suppressing gene expression or accessing siRNAs/oligonucleotides into the target cell was recognized in the art at the time the invention was made.

See page 275 of Schmidt, which teaches that “It can be notoriously difficult for oligonucleotides to penetrate cell membranes, and evade immune system attacks. Without solving the delivery problem, drug makers will be unable to deliver on RNAi’s therapeutic promise.”

In light of the teachings of Opalinska et al. and Schmidt, one of ordinary skill in the art would not have made and used the entire scope of the claimed invention solely based on the *in vitro* examples disclosed in the instant application. Since reduced expression of target transcripts in HeLa cells is not indicative of pharmaceutical effects or representative of *in vivo* methods, and

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since there is neither positive *in vitro* – *in vivo* correlation nor sufficient *in vivo* data, and since the general teachings in the art are such that nucleic acid-based therapeutics or *in vivo* use remain unpredictable, one of ordinary skill in the art would not have made and used the instantly claimed pharmaceutical composition with a resultant therapeutic effect at the time the invention was made.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

In view of the totality of the factors listed above, it is concluded that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with 1-8, 10-21, and 32-38.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 6, 9-10, and 38 are rejected under 35 U.S.C. 102(a) and (b) as being anticipated by Tijsterman et al. (*Science*, 2002, 295:694-697, also applicant's citation).

Note that the claims will remain rejected under 35 U.S.C. 102(a), even if applicant is granted the benefit of a prior-filed foreign priority.

The claims are drawn to a method a method for inhibiting the expression of a target transcript comprising contacting the target transcript with a single-stranded RNA molecule having a length of 15-29 nucleotides, wherein said expression is inhibited by RNA interference.

Tijsterman et al. teach a method for inhibiting the transcript of target gene GFP comprising contacting a single-stranded RNA molecule that is 25 nucleotides in length (page 695). They also teach a method of triggering RNAi with unc-22 antisense single-stranded RNAs (page 695). They teach that *in vivo* siRNAs are predominantly expressed as antisense RNAs and that first step of RNAi is bypassed by single-stranded antisense administration (pages 695-696). Furthermore, they teach that single-stranded antisense RNAs of at least 22 nucleotides and up to 40 nucleotides in length are capable of forming dsRNAs that become substrates for DICER-dependent degradation, therefore via RNAi (page 696).

Claims 1-4, 6, 9-10, and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Martinez et al. (*Cell*, 2002, 110:563-574, also applicant's citation).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-3, 6, 9-10, and 38 are described above.

Claim 4 is drawn to the method wherein said RNA molecule has a free 5'-hydroxyl moiety.

Martinez et al. teach a method of inhibiting target transcript expression with a 5'-phosphorylated single-stranded antisense RNA molecule of 19 to 29 nucleotides in length via RNAi mechanism both *in vitro* and *in vivo*. They teach that the single-stranded RNA contains a free 5' hydroxyl moiety. See entire reference. Accordingly, all the claim limitations are taught by Martinez et al.

Claims 1, 3-12, 16-21, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz et al. (*Nucleic Acids Research*, 2001, 29:415-422, citation of record).

The claims are drawn to a method for inhibiting the expression of a target transcript comprising contacting the target transcript with a single-stranded RNA molecule having a length of 15-29 nucleotides, wherein the RNA molecule is completely complementary to said target transcript, comprises a phosphate analogue that is phosphorothioate and at least one modified sugar-backbone or nucleobase-modified analogue, and said RNA molecule further comprising a cationic liposome and the method for inhibiting the expression of a target transcript is used for diagnostic, therapeutic applications for tumor diseases.

Schmitz et al. teach a method of inhibiting a target transcript, thymidylate synthase mRNA, with a single-stranded RNA molecule that is 18 or 30 nucleotides in length. They teach that the anti-thymidylate synthase antisense RNA molecule comprises 2'-O-methyl and phosphorothioates. They teach that antisense RNA molecules can be encapsulated in cationic

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liposomes to help increase cellular uptake and that chemical modifications help to increase stability against nucleases (page 421). They also teach that the antisense RNA molecule can be used in a clinical setting such as in a therapeutic method of treating human cancer (page 421). Note that the teachings of Schmitz et al. are as prophetic and enabled as the instant disclosure. Accordingly, all the claim limitations are taught by Schmitz et al.

Claims 1-13, 16-21, 33, and 37-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Zamore et al. (US 2004/0203145 A1).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The claims are drawn to a method of inhibiting target transcript expression with a single-stranded RNA molecule of 15-29 nucleotides, wherein the expression is inhibited by RNA interference, wherein said RNA comprises phosphate analogues such as 5'-phosphoramidates, said RNA is completely complementary to said target transcript, comprises at least one modified nucleotide analogue, the inhibition is *in vitro* and *in vivo*, and the RNA is complexed with cationic liposomes or biodegradable polymers for making a pharmaceutical composition, and said method is used for diagnostic or therapeutic applications for treatment of tumor diseases and autoimmune diseases.

Zamore et al. teach a method of reducing target transcript expression by 5'-phosphorylated single-stranded siRNAs *in vitro* and *in vivo* (paragraphs 0004-0005). They teach that chemically modified single-stranded siRNAs mediate RNAi with increased efficacy and that

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it is less costly to make single-stranded siRNAs than double-stranded siRNAs (paragraphs 0006, 0155). They teach that a 5' phosphate is required for RNAi in mammals and that containing a 5' hydroxyl group allows the single-stranded siRNAs to be phosphorylated (paragraphs 0135, 0138-0142). They teach that triphosphates are common and single-stranded siRNAs can comprise phosphate group analogs that function in the same manner as triphosphates (paragraph 0045). They teach that single-stranded siRNAs are less stable than double-stranded siRNAs and therefore introducing chemical modifications into the single-stranded siRNAs can help enhance their *in vivo* stability (paragraphs 0144, 0153). They teach that the single-stranded siRNAs comprise chemically modified nucleotides or nucleotide analogs wherein the 2'-OH and 3'-OH are replaced with various moieties such as alkyl, alkenyl, and alkynyl (paragraphs 0017-0018, 0039-0040). They teach that the single-stranded siRNAs also comprise modified phosphate groups by substituting one or more of the oxygens with sulfur such as phosphorodiamidates and phosphoroamidates because such modifications help decrease the rate of hydrolysis of the single-stranded siRNAs (paragraphs 0041-0042). They teach that the single-stranded siRNAs are sufficiently or completely complementary to a target mRNA and are about 10 to 50 or about 15 to 45, or about 19 and 40 nucleotides in length (paragraphs 0020, 0053-0054). They teach that the single-stranded siRNAs can be used to target pathogens such as tumor-associated or autoimmune-associated proteins, and therefore can be used in a diagnostic or therapeutic method by combining the single-stranded siRNAs with a pharmaceutically acceptable carrier such as liposomes and biodegradable polymers (paragraphs 0066, 0079-0107). Note that the extent to which directions/guidance/working examples are provided for *in vivo* methods of Zamore et al.

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are comparable to that provided in the instant application. Accordingly, all the claim limitations are taught by Zamore et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16, 20, 32-36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zamore et al. (US 2004/0203145 A1) as applied to 102(e) rejections above, further in view of Ts'o et al. (US 4,469,863).

Claims 1-13, 16, 20, 33, and 38 are described above.

Claims 14-15, 32, and 34-36 are drawn to a method of inhibiting target transcript expression by a single-stranded RNA molecule, wherein said RNA molecule is associated with

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biodegradable polymers via a covalent coupling at the 3' terminus of the RNA molecule, and said RNA molecule has 5'-moieties that are 5'-alpha-thiotriphosphate, 5'-alkylphosphonate, 5'-methoxymethylphosphonate, and 5'-alkyletherphosphonate.

As stated above, Zamore et al. teach a method of inhibiting target gene transcript expression with a single-stranded RNA molecule as claimed in claims 1-13, 16-21, 33, and 37-38 of the instant application. Zamore et al. further teach that methods for preparing pharmaceutical formulations are apparent to those skilled in the art (paragraph 0103). They teach that various chemical modifications for the 5' phosphate can be incorporated into the single-stranded RNA molecule and that single-stranded siRNAs can comprise phosphate group analogs that function in the same manner as triphosphates (paragraph 0045). Zamore et al. do not expressly teach 5'-alpha-thiotriphosphate, 5'-alkylphosphonate, 5'-methoxymethylphosphonate, and 5'-alkyletherphosphonate.

Ts'o et al. teach that alkyl or aryl phosphonate nucleotide analogues, such as methyl phosphonates, enable oligonucleotides to enter living cells intact and to bind the target sequence with specificity with an increased half-life, and therefore they are useful for regulating expression of cellular nucleic acids (columns 1, 17, 26-29).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate various 5' phosphate analogues or moieties to increase cellular uptake and stability of the single-stranded antisense RNA molecule as taught by Zamore et al. and Ts'o et al.

One of ordinary skill in the art would have been motivated to modify the single-stranded antisense RNA molecule of Zamore et al. by incorporating alkyl or aryl phosphonate nucleotide

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analogues of Ts'o et al., because Zamore et al. expressly teach the need to increase stability of the single-stranded antisense RNA molecule for more effective RNAi activity by incorporating chemical modifications (paragraphs 0144, 0153) and clearly suggest any phosphate group analogs that function in the same manner as triphosphates can be incorporated into the single-stranded antisense RNA molecule (paragraph 0045). Given these specific teachings, the skilled artisan would have been motivated to incorporate alkyl or aryl phosphonate nucleotide analogues into the single-stranded antisense RNA molecules of Zamore et al., with a reasonable expectation of success, because Ts'o et al. expressly teach that alkyl or aryl phosphonate nucleotide analogues increase specificity as well as stability of oligonucleotides (columns 1, 17, 26-29). Further, applicant's attention is directed to the fact that the different species of 5' moieties claimed in claims 32 and 34-36 were originally claimed in a Markush-type language, which reflects that the independently claimed 5' moieties are indeed related chemical species with shared core structure and function. In view of the foregoing, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner
Art Unit 1635